44. The method of claim 43, wherein said core sequence is SEQ ID NO: 7.

45. The method of claim 35, wherein said T-cell epitope peptides are analog peptides in which one or more amino acids of the T-cell epitope peptides are substituted.

46. The method of claim 45, wherein said analog peptide has the amino acid sequence of SEQ ID NO: 14.

47. The method of claim 35, which further comprises a pharmaceutically acceptable carrier or diluent.

48. The peptide-based immunotherapeutic agent of claim 1, wherein said T-cell epitope peptides are analog peptides in which one or more amino acids of the T-cell epitope peptides are substituted.

Remarks

Claims 1, 3-7, and 10-30 are currently pending and before the Examiner for consideration. Claims 8-9 and 27-30 stand withdrawn from consideration. By this amendment, claims 1, 4, and 6 have been amended, claims 3, 7-12, and 18-30 have been canceled, and new claims 31-47 have been added. Support for the amendments to the specification and claims may be found in the specification as indicated in the attached Table A.

The subject invention provides a unique and advantageous peptide-based immunotherapeutic agent comprising linear multi-epitope peptides joined together and wherein said multi-epitope regions are derived from different cedar pollen allergens. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Applicants wish to thank SPE Chan for the courtesy of the interview discussing the declaration/power of attorney submitted on November 6, 2000. As discussed in the interview, the declaration was prepared as directed by the MPEP in Chapter 200. Further, as discussed in the interview, Applicants filed the subject application on September 9, 1998. The confusion regarding

the filing date appears to center on the 102(e) date assigned this application, which is January 4, 1999. As a result of the interview, it is the understanding of Applicants that the declaration filed on November 6, 2000 is acceptable and that the requirement for a new declaration has been withdrawn. Applicants respectfully request confirmation of this understanding.

Claims 1, 4-6, 13, and 17 have been rejected under 35 U.S.C. § 112, first paragraph, as having new matter. Applicants respectfully submit that this issue is moot in view of the amendments to the claims and Table A which provides support for the amendments.

Claim 13 has been rejected as being indefinite under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants believe that the amendments made to the claims have satisfied this issue. Support for the amendment may be found, for example, in Example 14, page 40.

Claim 1 has been rejected as being indefinite. This issue is moot in view of the amendment to the claim.

Claims 6, 11, 12, 23, and 24 have been rejected as being indefinite in the recitation of "contains an amino acid sequence described in any of SEQ ID NO:", because it is not clear what is meant. Applicants' believe that this issue has been addressed by the amendments made to the claims.

Claims 1, 4-6, 13, and 17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers *et al.* in view of WO 94/01560 and further in view of Hashiguchi *et al.* or Komiyama *et al.* or WO 94/11512 and Wallner *et al.* Applicants respectfully traverse the rejection on the following grounds. Applicants' respectfully submit that Rogers *et al.* fails to teach polypeptides which do not substantially react with IgE antibodies found in the sera of allergic patients. As demonstrated in Figure 3 of Rogers *et al.*, the peptide constructs 11-12-13 and 13-11-12 react, substantially, with the allergic sera containing IgE antibodies. These peptide constructs reacted with sera from other five patients (see page 961, 16-18 lines from the bottom of column 1). In contrast, as shown in the accompanying declaration, there is no significant statistical difference, with a significant level of 5%, by Student's t-test between the reactivity of the six multi-epitope peptides

of the present invention (C.A.#1 to C.A.#6) with sera of 21 cedar pollinosis patients and that with sera of 8 healthy subjects.

Claims 1, 4-6, 13, and 17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers *et al.* in view of WO 94/01560 and further in view of Hashiguchi *et al.* or Komiyama *et al.*, or WO 94/11512 and Wallner *et al.* Applicants respectfully traverse the rejection on the following grounds. It is respectfully submitted that the combination of references fails to provide teaching, suggestion, or motivation to combine the references and that the currently applied obviousness rejection is the result of improper hindsight reconstruction of the presently claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Therefore, "[w]hen determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *In re Beattie*, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (quoting *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). In the case of the instantly claimed invention, it is submitted that the references, themselves, are devoid of any teaching, suggestion, or motivation to combine.

While Rogers *et al.* suggest that the methods and approaches taught within the reference may be applicable to the combination of multiple T-cell epitopes from one or more antigens into a single polypeptide chain (paragraph bridging pages 964-965), there is absolutely no suggestion to construct multi-epitope T-cell peptides having the currently recited properties nor is there a recognition that such peptides could be constructed. The reference further fails to teach multi-epitope peptides which [a] have minimum core sequences (as required in claims 13 and 43), [b] have the minimum core sequence of claims 14 and 44, [c] have the amino acid sequence of claims 16 and 46, [d] do not contain cysteine (claims 31 and 38), or [e] have the amino acid sequences of claims 34 and 42.

Hashiguchi *et al.*, WO 94/01560, Komiyama *et al.*, WO 94/11512 and Wallner *et al.* fail to remedy these defects in the primary reference. According to the Office Action at pages 4-6, the secondary references have been cited to teach T-cell epitopes of cry j 1 and cry j 2 as well as the diversity of the human population with respect to its HLA haplotype. While WO 94/01560 teaches linear polypeptides of at least two cry j 1 T-cell epitopes, the reference fails to teach or suggest that these linear polypeptides should be combined with T-cell epitopes of cry j 2. Further, reliance upon this reference with respect to the selection of peptides on the basis of high positivity indices is unwarranted since selection of peptides on the basis of high positivity indices alone would not lead to peptides having the recited characteristics. As discussed in the specification at page 23, lines 20-23, the high positivity index alone cannot increase efficiency if the HLA class II molecules presenting the antigens are the same.

Hashiguchi *et al.*, WO 94/11512, and Komiyama *et al.* teach purified cry j 2 antigens and T-cell epitopes thereof. These references, likewise, fail to teach or suggest that T-cell epitopes of cry j 2 should be joined with T-cell epitopes of cry j 1 to form a multi-epitope peptide comprising T-cell epitopes from these two allergens.

It is also respectfully submitted that the combination of references fails to teach, suggest, or provide any motivation to construct the peptide-based immunotherapeutic agent of claim 1. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Because the combination of references fails to establish any motivation to combine, and because all limitations of the claim have not been met by the combination of references, it is respectfully submitted that a *prima facie* case of obviousness has not been made and that the rejection should, therefore, be withdrawn.

Applicants also respectfully submit that the rejection is also the result of improper hindsight reconstruction of the claimed invention. While applicants recognize that such a reconstruction of the invention is proper so long as an obviousness rejection takes into account only the knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made, and does not include knowledge gleaned only from applicant's disclosure (*In re McLaughlin*, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971)), it is respectfully submitted that applicants'

disclosure has been used to serve as the basis of the rejection currently of record. Combining prior art references without evidence of a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). Additionally, the Court of Customs and Patent Appeals has stated, "[i]n determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Again, in the case of the presently claimed invention, it is unclear what motivation one of ordinary skill in the art would have had to apply the cited teachings without the guidance and disclosure of the presently claimed invention. The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). In order to establish a case of *prima facie* obviousness, it is incumbent upon the Patent Office to determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus. *See, e.g., In re Ochiai*, 71 F.3d 1565, 1569-70, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); *In re Deuel*, 51 F.3d 1552, 1557, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995) ("[A] prima facie case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art." (emphasis in original)); *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1991); *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). *See also, In re Kemps*, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996) (discussing motivation to combine). It is respectfully submitted that the Office Action derived the required motivation to combine from the disclosure and

teachings of the instant specification, not from the references applied against the claims. Accordingly, it is respectfully submitted that the obviousness rejection of record has improperly utilized the disclosure of these inventors as a blueprint for piecing together the prior art to defeat patentability and the withdrawal of the rejection is respectfully requested.

In view of the foregoing remarks and the amendments to the claims, the applicants believe that the pending claims are now in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§ 1.16 or 1.17, as required by this paper, to Deposit Account 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/jaj

Attachment: Petition and Fee for Extension of Time Under 37 C.F.R. § 1.136(a)
Table A
Declaration Under 37 C.F. R. § 1.132

TABLE A

REVISION	SUPPORT IS FOUND IN SPECIFICATION
Claim 1(a)	Corresponds to Claim 3, Which Is Now Cancelled.
Claim 1(b)	Example 7, Pages 30-32 of the Specification, and Fig. 8
Claim 1(c)	Example 8 on Pages 32-33 of the Specification and Fig. 9
Claim 1(d)	Page 15, lines 15-19 and Example 9 on Pages 33-35 of the Specification, and Fig. 11
Claim 31 (New)	Page 11, Lines 7-15 of the Specification
Claim 33 (New)	Fig. 3 and Fig. 4
Claims 35-47 (New)	Directed to the Method Claims Corresponding to Pending Claims 1, 3-6, 13-17, and 31-34
Claims 45 & 48 (New)	Page 15, line 23 through Page 16, line 19.
Specification,	Correction of Typographical Errors
Page 3, Line 6;	Correction of Typographical Errors
Page 7, line 23;	Insert genus and species for short ragweed.
Page 8, line 1;	Provide genus and species for juniper and mountain cedar.
Page 8, Lines 7;	Correction of Typographical Errors
Page 8, Line 22;	Correction of Typographical Errors
Page 12, Line 7	Correction of Typographical Errors
Page 23, Line 16	Correction of Typographical Errors
Page 30, Line 8	Correction of Typographical Errors
Page 31, Line 7	Correction of Typographical Errors
Page 31, Line 17	Correction of Typographical Errors
Page 34, Line 17	Correction of Typographical Errors
Specification, Page 12, Line 1	Page 12, Line 7 of the Specification and Fig. 2
Specification, Page 17, Lines 5-6	Page 11, Lines 16-24 of the Specification
Specification, Page 38, Line 2	Page 39, Line 4 of the Specification